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Research Article

A PROSPECTIVE COHORT STUDY ON EFFECT OF LEVOTHYROXINE REPLACEMENT ON HEALTH RELATED QUALITY OF LIFE IN SUBJECTS WITH SUBCLINICAL HYPOTHYROIDISM IN A TERTIARY CARE CENTRE OF INDIA

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ABSTRACT

Objectives: To evaluate the impact of Levothyroxine replacement on health related quality of life (QoL) in subjects with subclinical hypothyroidism.

Materials and methods: In this hospital based open labeled randomized double-blind study, patients were assigned either to treatment with Levothyroxine (n = 50) or were controls (n =50).In addition to the clinical and biochemical parameters, Health related Quality of Life(Hr QoL) was assessed by means of three questionnaires-the SF-36(version 2),Underactive Thyroid Symptom Rating Questionnaire(ThySRQ) and Thyroid Treatment Satisfaction Questionnaire(ThyTSQ) at baseline before intervention, at six weeks and at twelve weeks follow up visits following intervention.

Results: All subscales of the general health status measure, the SF-36v2 tended towards an improvement with Levothyroxine therapy particularly in the domain "role pain" where the improvement was marked and pronounced. Control arm showed no improvement in any of the subscales at 6 or 12 weeks follow up. ThySRQ showed a significant decrease in frequency and the perceived severity in subjects receiving Levothyroxine. Tiredness was the most improved symptom. However, there was no improvement rather a deterioration of scores in the control group. ThyTSQ scores also demonstrated a noticeable satisfaction in the scores after Levothyroxine supplementation at 6 weeks, which intensified further at 12 weeks visit.

Conclusion: In subjects with Subclinical Hypothyroidism, substitution with Levothyroxine results in a significant improvement in Health related Quality of life (HrQoL): General Tool (SF36v2 –all subscales) and thyroid disease specific tools (ThySRQ & ThyTSQ)

INTRODUCTION

Subclinical hypothyroidism (SCH) is a commonly encountered biochemical finding in clinical practice, characterized by elevated levels of thyroid stimulating hormone (TSH) in serum in the presence of normal serum levels of free thyroxine (FT4), as compared with population-based reference ranges for these values[1]. Overall, the population prevalence of subclinical hypothyroidism is around 12–18%, the diagnosis being more common in women and elderly population and is higher in white than in black populations[2, 3]. Subclinical Hypothyroidism (SCH) is a common condition affecting 6–17% of the Indian population[4]. Although considered an asymptomatic disorder, some patients may present with nonspecific symptoms, suggestive of overt hypothyroidism[5]. Earlier studies had also reported higher prevalence of cognitive dysfunction, anxiety and depression among subjects with SCH[6].It is still controversial whether treatment with Levothyroxine reverses this risk. Furthermore, it is uncertain whether Levothyroxine therapy improves symptoms of hypothyroidism or health status in SCH. In patients with TSH <10 mIU/L, a diagnosis of SCH is usually not treated with Levothyroxine (LT4) supplementation. As per the latest guidelines, a decision for treatment is based on the presence of mild symptoms and signs suggestive of hypothyroidism including goiter and presence of other co morbidities and special situations like infertility and pregnancy[7]. Patient who does not fulfill these criteria are usually followed up at regular intervals. Health related Quality of life (QoL) is a subjective measure of assessment of the impact of the disease and its management on the physical, mental, social and somatic components of health of an individual. Thus, it is an important supplementary outcome tool for the assessment of different medical conditions. Previous studies have enlightened that QoL is frequently hampered in

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patients with overt hypothyroidism [8]. However, the influence of Subclinical Hypothyroidism (SCH) on health status or quality of life (QoL) is not yet well established. Some population studies showed no differences in health-related QoL perception between SCH patients and a normal, healthy population[9, 10], while another outpatient study demonstrated impairment in SCH compared with normal controls[11]. Although there have been studies evaluating the clinical and biochemical parameters along with assessment of the quality of life in subclinical hypothyroidism in the western population, there is paucity of similar studies in Indian subcontinent.

The aim of our study is to evaluate the impact of Levothyroxine supplementation and restoration of euthyroidism on health related quality of life (QoL) in patients with persistent SCH with TSH <10 mIU/L.

MATERIALS & METHODS

The study was a hospital based open label randomized cross sectional study. All patients attending the outpatient clinic of Department of Endocrinology, Nilratan Sircar Medical College, Kolkata, West Bengal and fulfilling the inclusion and exclusion criteria were included in the study. The inclusion criteria was all subjects having two laboratory serum determinations showing serum Thyrotropin (TSH) levels above 4.0 mIU/mL but less than 10 mIU/mL and free thyroxine (FT4) in the normal range (0.9-1.8 ng/dL) at least 6 weeks apart aged between 18 and 60 years of both genders. However, subjects with a past history of hypothyroidism who received Levothyroxine supplementation, iatrogenic subclinical hypothyroidism as a consequence of radio iodine treatment or surgery for hyperthyroidism due to any cause, known history of chronic disease of cardiovascular, renal or hepatic aetiology, known history of psychiatric illness, Type 2 Diabetes Mellitus or dyslipidemia and patients with past or present history of receiving medications which can affect thyroid function were excluded from the study. The duration of the study was 18 months. The study protocol was approved by Institutional Ethics Committee. Informed consent was taken from all the participants prior to commencement of the study.

A total of 100 participants were randomized into two groups by a software generated chart with 1:1 allocation. Subjects belonging to the first group received 25 to 50 *u*g of L-thyroxine (based on body weight) for 12 consecutive weeks. [Target TSH: 2-4 mIU/mL].Subjects belonging to the other group were controls. All the participants asked to revisit after six weeks of baseline visit for any dose adjustment if necessary and evaluation of the study protocol. A reevaluation of the clinical examination with biochemical parameters and relevant validated questionnaires was done after twelve weeks of baseline visit. The Quality of Life Assessment (QoL) was performed by means of the following Questionnaires':

SF-36(Version 2) [12]**:** The SF-36 (Medical Outcomes Study 36-Item Short Form Health Survey) was used to assess the QoL of the population being studied. The SF-36 is a generic QoL assessment instrument composed of 36 items, divided into eight scales or dimensions-physical function, general health(GH), vitality, mental health(MH), social function(SF), role emotional(RE), role physical(RP) and bodily pain(BP). Answers were presented on a Likert scale. Each scale can range from zero (0) to hundred (100) points, in which 100 points represents the maximum score and the best satisfaction while zero points represents the lowest score and the highest dissatisfaction with QoL.

Underactive Thyroid Symptom Rating Questionnaire (ThySRQ)[13]*:* The ThySRQ has 15 symptoms with a 4-point symptom bother scale measuring perceived symptom severity, and respondents provide a bother rating for applicable symptoms, indicating how much the symptom bothers them from not at all, a little, quite a bit, very much (scoring 0,1,2 and 3 respectively). IF any patient reports that they do not have a symptom are given a symptom bother rating of zero (not at all bothered)

Thyroid Treatment Satisfaction Questionnaire (ThyTSQ)[14]*:* The ThyTSQ has seven items including questions about satisfaction with current treatment, and control of symptoms of underactive thyroid. Instructions ask patients to consider their experience of treatment for underactive thyroid over the previous few weeks. Patients respond to each item by circling a number on a scale from 6 to 0 (where 3 is considered a neutral option), indicating their degree of satisfaction with that aspect of treatment.

The order of questionnaire administration in every visit was as follows: SF-36v2, ThySRQ, and ThyTSQ.

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ±SD and results on categorical measurements are presented in Number (%). Significance is assessed at a level of 5%. Normality of data was tested by simultaneous Anderson Darling test, Shapiro-Wilk test and graphically by QQ plot. Friedman's ANOVA with post-hoc Dunnet's test method has been used to find the significance of study parameters measured on three occasions between same or related groups of subjects. The $p<0.05$ was considered statistically significant. The Statistical software namely SAS Version 9.2 for Windows, Statistical Package for Social Sciences (SPSS) Version 21.0 for windows were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc. The Statistical software namely SAS Version 9.2 for Windows, Statistical Package for Social Sciences (SPSS) Version 21.0 for windows were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs and tables.

RESULTS

The baseline demographic, clinical and biochemical characteristics of the patients are listed in Table 1. There were no significant differences of baseline characteristics between the two groups at randomization. The mean age was 43.8±12.6 years. Our study showed a female predilection with 82 females(82%)[42 in Levothyroxine arm and 40 in the control arm] and 18 males(18%).Sixty four percent of the patients included in our study was positive for Anti Thyroid Peroxidase(TPO)antibodies(36 in L-thyroxine arm and 28 in control arm).Only eight of the study participants were smokers(8%).Following intervention, statistically significant decrease in the TSH levels were recorded in Levothyroxine arm($p<0.001$) unlike the placebo arm($p=0.15$).

Table 1 Baseline demographic characteristics of study sample

Parameter	All patients (n=100)	Levothyroxine (n=50)	Control(n=50)	P value
Age(yrs) [Mean±SD]	43.8±12.6	43.5±13.3	44.2±12.1	0.25
Male(n) (%)	18	8	10	0.13
Weight(kg)	59.88±16.4	59.86±8.96	59.88±7.7	0.51
BMI(kg/m^2)	24.74±1.9	24.44±2.31	24.73±2.2	0.68
Waist Hip Ratio	0.87±0.1	0.86±0.03	0.88±1.03	0.59
SBP(mm of Hg)	126.8±5.5	127.2±5.77	125.64±4.86	0.74
DBP(mm of Hg)	78.14±4.2	78.8±4.44	77.52±3.99	0.77
TSH(mIU/ml)	7.85±1.24	7.9±1.25	7.83±1.23	0.52
FT4(ng/dl)	1.05±0.22	1.24±0.21	1.23±0.22	0.75
Anti TPO Antibody (%)	64	36	28.	0.68

n (%) for categorical variables, Mean±SD for continuous variables. BMI-body mass index, SBP-systolic blood pressure, DBP-diastolic blood pressure, TSH: Thyroid stimulating hormone, Ft4-free T4, TPO-thyroid Peroxidase SD: Standard deviation.

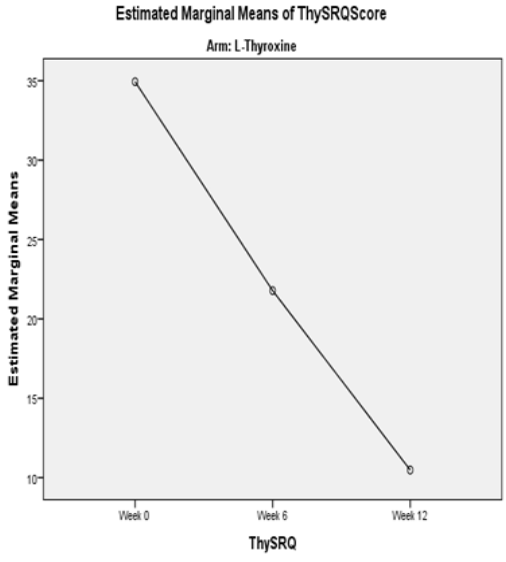
Table 2 Changes in thyroid function tests in both the groups

Parameter	L Thyroxine(n=50)			p value	Control(n=50)			p value
	0 weeks	6 weeks	12 weeks		0 weeks	6 weeks	12 weeks	
TSH(Miu/ml)	6.90	3.41	1.90	<0.001	6.83	6.91	7.12	0.15
FT4(ng/dl)	1.24	1.30	1.41	0.001	1.23	1.22	1.2	0.2
FT3(pg/ml)	3.31	3.49	3.58	0.001	3.30	3.30	3.29	0.19

Table 3 Changes in Thy SRQ Score

Thy SRQ Score						
Arm		N	Mean	Std. Deviation	Minimum	Maximum	P*
Levothyroxine	Thy SRQ-0 weeks	50	34.94	3.401	28	42	**<0.001**
	Thy SRQ- 6 weeks	50	21.78	2.597	17	27	
	Thy SRQ-12 weeks	50	10.48	2.197	7	14	
Placebo	Thy SRQ-0 weeks	50	34.94	2.773	28	40	**<0.01**
	Thy SRQ- 6 weeks	50	35.38	2.338	30	40	
	Thy SRQ-12 weeks	50	36.34	2.037	31	41	

P computed by Friedman's ANOVA, p* is between baseline and week 12



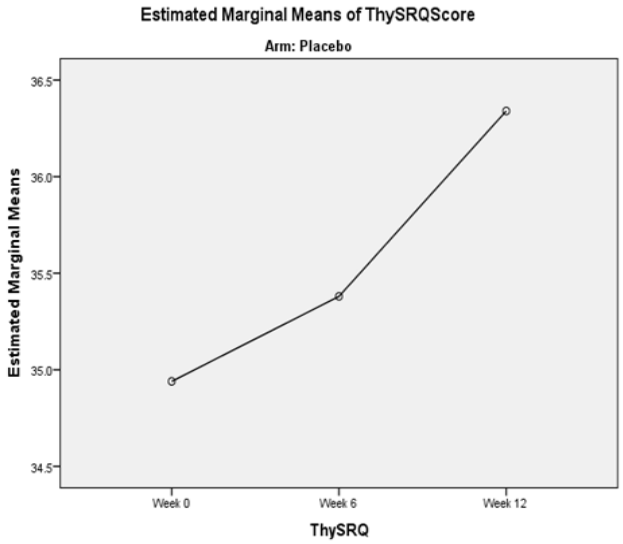


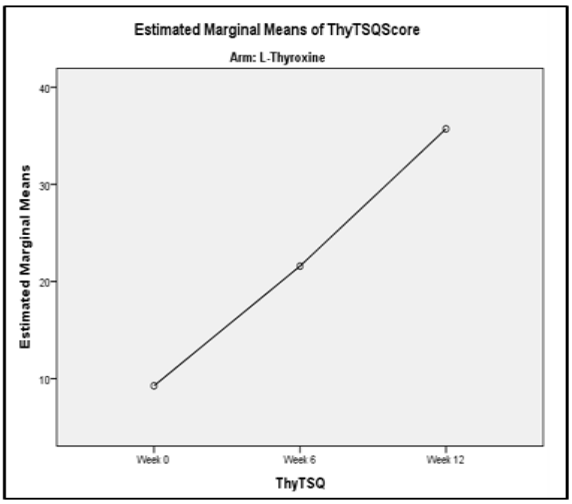
Table 4 Changes in Thy TSQ Score

Thy TSQ Score							
Arm		N	Mean	Std. Deviation	Minimum	Maximum	p*
Levothyroxine	ThyTSQ- 0 weeks	50	9.26	1.827	6	14	**<0.001**
	ThyTSQ- 6 weeks	50	21.58	3.535	15	29	
	ThyTSQ-12 weeks	50	35.72	2.921	29	41	
Placebo	ThyTSQ- 0 weeks	50	9.20	1.414	6	12	**<0.001**
	ThyTSQ- 6 weeks	50	8.80	1.309	6	12	
	ThyTSQ-12 weeks	50	8.38	1.369	5	11	

P computed by Friedman's ANOVA Based on estimated marginal means , p* is between baseline and week 12

In addition there was a significant increment in Free T4(p=0.001) and Free T3(p=0.001) thyroid hormone levels in the Levothyroxine arm in contrast to the placebo arm where no significant differences were noticed in either free T4(p-0.2 or Free T3(p-0.19) levels (Table 2).

Each of the quality of life (QoL) questionnaires of both Levothyroxine and control groups and their changes during the first and second follow up visits at six and twelve weeks respectively are being discussed separately (Tables 5-12).



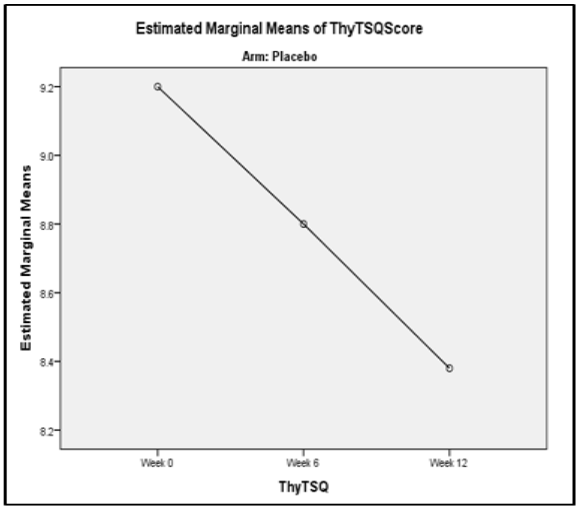
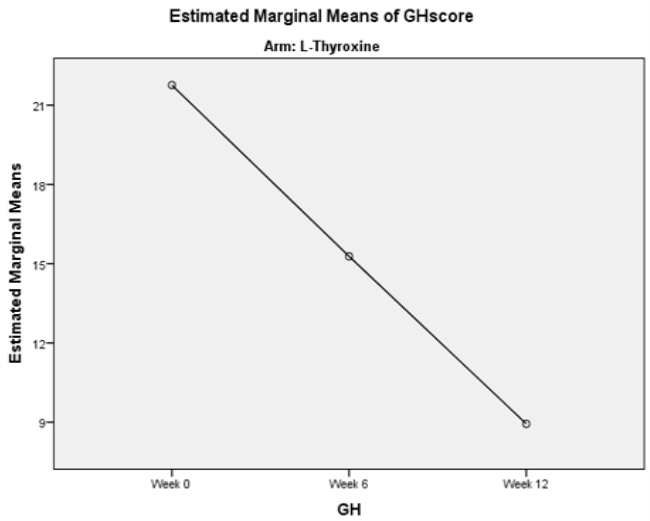


Table 5 Changes in General Health (GH)

Change in GH Score							
Arm		**N**	**Mean**	**Std. Deviation**	**Minimum**	**Maximum**	**P***
Levothyroxine	GH - 0 week	50	21.76	1.572	19	25	0.001
	GH-6 weeks	50	15.28	1.457	12	19	
	GH-12 weeks	50	8.94	1.789	5	13	
Placebo	GH - 0 week	50	21.76	1.572	19	25	0.002
	GH-6 weeks	50	22.16	1.283	20	25	
	GH-12 weeks	50	22.98	1.237	20	25	

P computed by Friedman's ANOVA, p* is between baseline and week 12



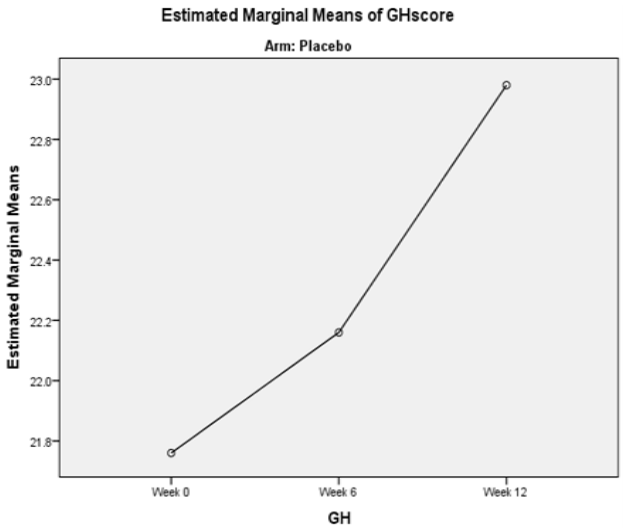


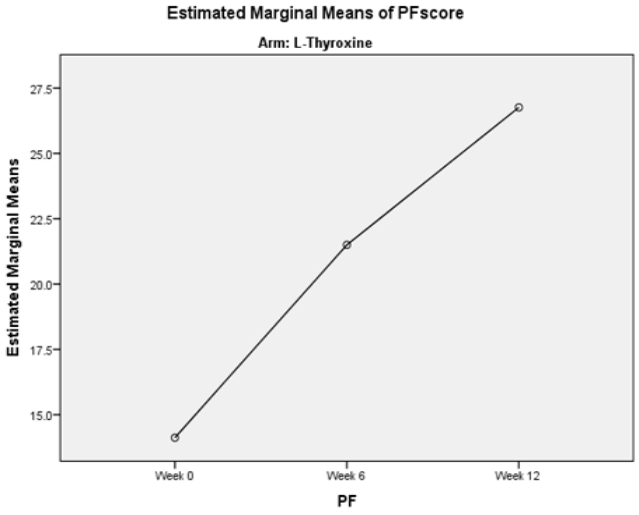
Table 6 Change in Physical Function (PF)

Descriptive Statistics							
Arm		N	Mean	Std. Deviation	Minimum	Maximum	P*
Levothyroxine	PF- 0 week	50	14.12	1.769	10	18	**<0.001**
	PF- 6 weeks	50	21.50	1.753	18	25	
	PF-12 weeks	50	26.76	1.451	24	29	
Placebo	PF- 0 week	50	14.16	1.695	11	18	**<0.001**
	PF- 6 weeks	50	13.44	1.431	10	16	
	PF-12 weeks	50	12.66	1.287	10	15	

P computed by Friedman's ANOVA, p* is between baseline and week 12

As shown in Table 5 and the corresponding figure, the underactive Thyroid symptom response questionnaire (ThySRQ) revealed that the frequency and the perceived severity decreased significantly in subjects receiving Levothyroxine. Improvement of scores started at 6 weeks which intensified at 12 weeks follow up visit.

The mean scores in the Levothyroxine arm decreased from 34.94 to 10.48 after twelve weeks with a 70% improvement in the scores after twelve weeks i.e. second baseline visit ($p<0.01$)**.**The minimum and maximum scores in Levothyroxine arm at 0 weeks were 28 and 42 respectively which drastically reduced to 7 and 14 respectively at the end of 12 weeks.



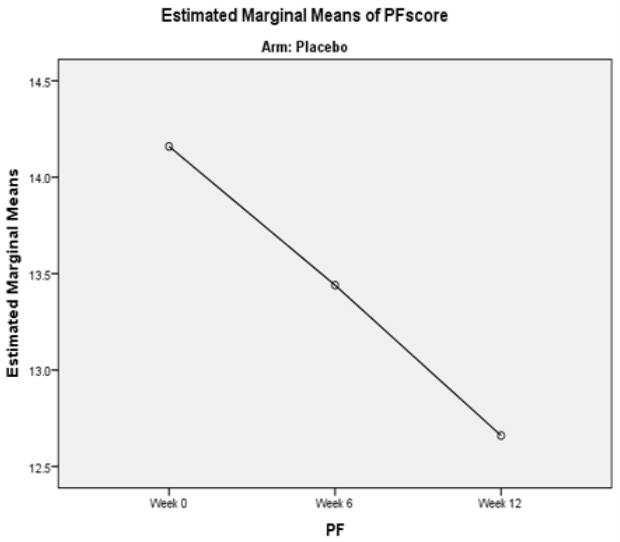
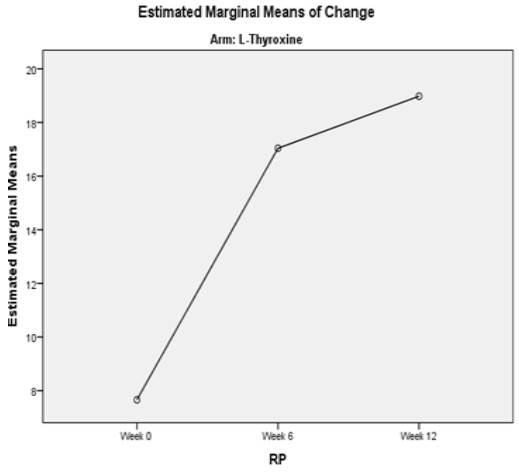


Table 7 Change in Role Physical (RP)

Descriptive Statistics							
Arm		**N**	**Mean**	**Std. Deviation**	**Minimum**	**Maximum**	**p***
Levothyroxine	RP- 0 week	50	7.66	1.686	4	11	**<0.001**
	RP - 6 weeks	50	17.04	1.428	13	19	
	RP-12 weeks	50	18.98	.820	17	20	
Placebo	RP- 0 week	50	7.66	1.686	4	11	**<0.001**
	RP - 6 weeks	50	7.52	1.607	4	11	
	RP-12 weeks	50	7.42	2.843	4	24	

P computed by Friedman's ANOVA p* is between baseline and week 12



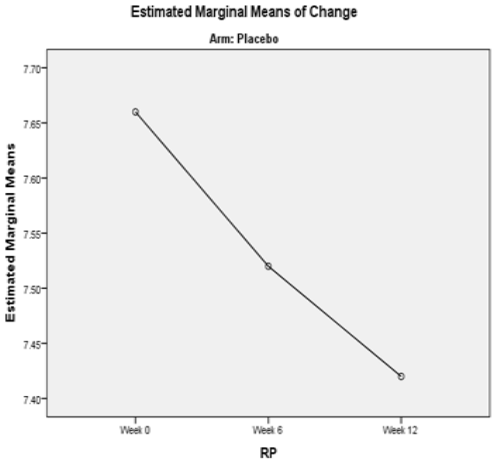


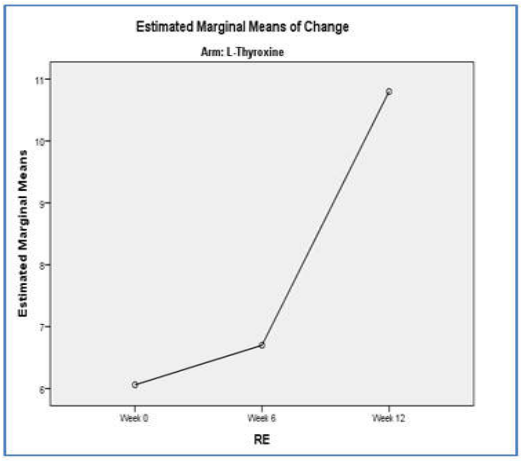
Table 8 Change in Role Emotional (RE)

Descriptive Statistics							
Arm		**N**	**Mean**	**Std. Deviation**	**Minimum**	**Maximum**	**P***
Levothyroxine	RE- 0 week	50	6.06	1.420	4	9	<0.001
	RE- 6 weeks	50	6.70	1.165	5	9	
	RE-12 weeks	50	10.80	1.773	9	16	
Placebo	RE- 0 week	50	6.06	1.420	4	9	<0.001
	RE- 6 weeks	50	6.04	1.399	4	9	
	RE-12 weeks	50	5.56	1.358	3	8	

P computed by Friedman's ANOVA p* is between baseline and week 12

Pair wise comparisons revealed a significant p values between 0 and 6 weeks ($p<0.001$) and 0 and 12 weeks ($p<0.001$). Thyroid treatment satisfaction questionnaire (ThyTSQ) demonstrated a noticeable satisfaction in the scores after Levothyroxine supplementation at 6 weeks, which improved further at 12 weeks. In contrast the scores decreased slightly in the control arm.

The changes in both the arms were found to be statistically significant (Table 6 and corresponding figure). The minimum and maximum scores in Levothyroxine arm at 0 weeks were 6 and 14 respectively which remarkably escalated to 29 and 41 respectively at the end of 12 weeks. On the contrary, the minimum and maximum scores in the control arm at 0 weeks were 6 and 12 respectively which decreased slightly to 5 and 11 respectively at the end of 12 weeks.



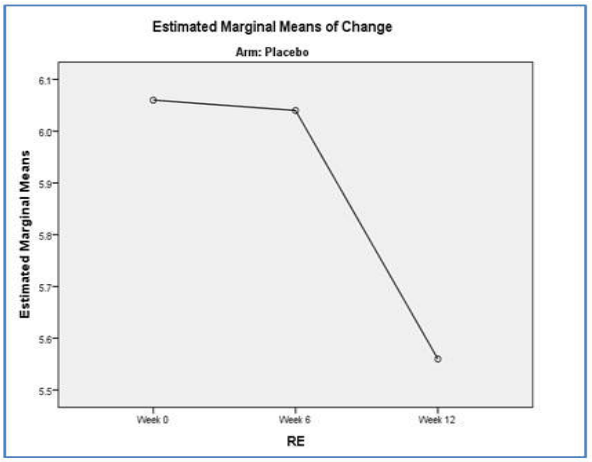
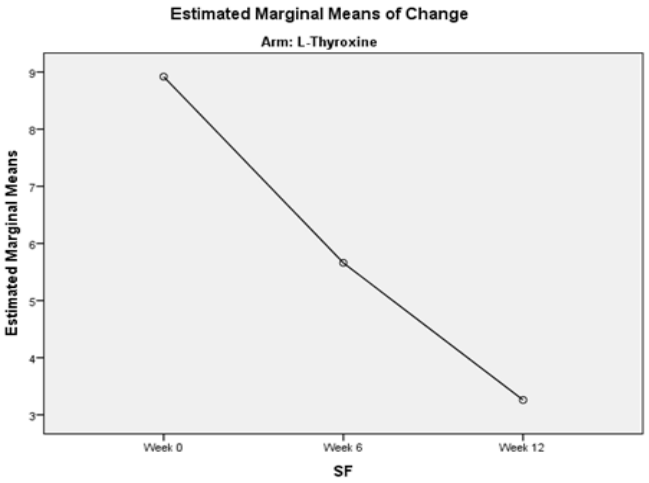


Table 9 Change in Social Function (SF)

Descriptive Statistics							
Arm		**N**	**Mean**	**Std. Deviation**	**Minimum**	**Maximum**	**P***
Levothyroxine	SF- 0 week	50	8.92	.804	8	10	**<0.001**
	SF- 6 weeks	50	5.66	.982	4	7	
	SF-12 weeks	50	3.26	.751	2	5	
Placebo	SF- 0 week	50	8.92	.804	8	10	**<0.001**
	SF- 6 weeks	50	8.94	.793	8	10	
	SF-12 weeks	50	9.06	.998	4	10	

P computed by Friedman's ANOVA ,p* is between baseline and week 12



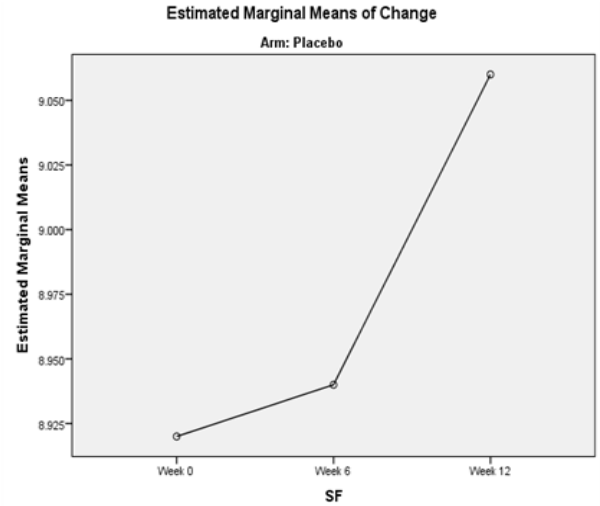


Table 10 Change in Bodily Pain (BP)

Descriptive Statistics							
Arm		**N**	**Mean**	**Std. Deviation**	**Minimum**	**Maximum**	**P**
Levothyroxine	BP- 0 week	50	8.94	.793	8	10	**<0.001**
	BP- 6 weeks	50	5.66	.982	4	7	
	BP-12 weeks	50	3.06	.712	2	4	
Placebo	BP- 0 week	50	8.94	.793	8	10	**0.002**
	BP- 6 weeks	50	9.10	.763	6	10	
	BP-12 weeks	50	9.64	.598	8	10	

P computed by Friedman's ANOVA p* is between baseline and week 12

The changes in both the arms were found to be statistically significant ($p<0.001$) Pair wise comparisons revealed a significant p values between 0 and 6 weeks ($p<0.001$) and 0 and 12 weeks ($p<0.001$) in the Levothyroxine arm. The present study also revealed that Indian patients with subclinical hypothyroidism experienced significant QoL reductions in all of the eight SF36 subscales of the general health status measure, the SF-36v2 - general health(GH),physical function(PF),role physical(RP), role emotional(RE),social function(SF), bodily pain(BP),vitality and mental health(MH). In our study(Tables 5-12 and the corresponding figures), all the subscales tended towards an improvement with Levothyroxine therapy, particularly in the domain "role pain" where the improvement was marked and pronounced. The improvement began to be noticeable at six weeks visit which intensified further at twelve weeks follow up visit .In comparison to the other subscales; there were relatively lesser improvement in "mental health" and "role emotional" subscales. In contrast, the control arm showed no improvement in any of the subscales at 6 or 12 weeks follow up visits, rather it showed a deterioration in scores "role pain", "vitality", "role emotional" scores.

DISCUSSION

Subclinical hypothyroidism (SCH) is a commonly encountered biochemical finding in clinical practice, characterized by elevated levels of thyroid stimulating hormone (TSH) in serum in the presence of normal serum levels of free thyroxine (FT4), as compared with population-based reference ranges for these values[1]. Although considered an asymptomatic disorder, some patients may present with nonspecific symptoms, suggestive of overt hypothyroidism[5]. Health related Quality of life (QoL) is a subjective measure of assessment of the impact of the disease and its management on the physical, mental, social and somatic components of health of an individual. Thus, it is an important supplementary outcome tool for the assessment of different medical conditions. Previous studies have enlightened that QoL is frequently hampered in patients with overt hypothyroidism [8]. However, the influence of Subclinical Hypothyroidism (SCH) on health status or quality of life (QoL) is not yet well established. Some population studies showed no differences in health-related QoL perception between SCH patients and healthy population[9, 10], while another outpatient study demonstrated impairment in SCH compared with normal controls[11]. Although there have been studies evaluating the clinical and biochemical parameters along with assessment of the quality of life in subclinical hypothyroidism in the western population, there is paucity of similar studies in Indian subcontinent.

In the present study, the effects of Levothyroxine replacement in subjects with subclinical hypothyroidism were assessed in comparison with controls in a hospital based open labeled randomized prospective study. Quality of life (QoL) was assessed by means of three pretested and validated questionnaires- a generic tool (SF36v2) and two diseased organ specific questionnaires namely Underactive Thyroid Symptom Rating Questionnaire (ThySRQ) and Thyroid treatment symptom questionnaire(ThyTSQ): In this study, all the subscales of the general health status measure, the SF-36v2 tended towards an improvement with Levothyroxine therapy, particularly in the domain "role pain" where the improvement was marked and pronounced. The improvement began to be noticeable at six weeks visit which intensified further at twelve weeks follow up visit .In comparison to the other subscales; there were relatively lesser improvement in "mental health" and "role emotional" subscales. In contrast, the control arm showed no improvement in any of the subscales at 6 or 12 weeks follow up visits, rather it showed a deterioration in scores "role pain", "vitality", "role emotional" scores. Our results showed that even mild doses of Levothyroxine replacement was significantly associated with the improvement of physical performance, vitality and mental health found in untreated SCH. An increase of SF-36 questionnaire scores showed a positive correlation with the increment of thyroid hormone levels. According to an Italian study, Bianchi *et al*. reported that 81 patients with subclinical hypothyroidism experienced significant reductions in seven of the eight SF-36 subscales[15]. Winther *et al*, in another prospective cohort study revealed that 78 patients with autoimmune hypothyroidism experienced significant reductions in seven of the eight SF-36 scales.[16]The study also revealed that the patients experienced significant improvements in the SF-36 scales for role vitality, bodily pain, physical functioning, social functioning, and mental health at 6 months after commencing Levothyroxine therapy. Another crossover trial revealed that SF-36 scores were significantly reduced at baseline and during the euthyroid and subclinical hypothyroid phases.[17] Furthermore, a study which included 100 patients with subclinical hypothyroidism revealed significant reductions in all eight SF-36 subscales[18] and similar findings of poor QoL have been revealed in other studies of patients with Hypothyroidism.[19,] In contrast with the above findings are results from the study that included elderly subjects and reported that SCH is not clearly associated with cognitive impairment, depression or poor quality of life (QoL)[20].

To our knowledge, the underactive Thyroid symptom response questionnaire (ThySRQ) revealed that the frequency and the perceived severity decreased significantly in subjects receiving Levothyroxine. Improvement of scores started at 6 weeks which intensified at 12 weeks follow up visit. The mean scores in the Levothyroxine arm decreased from 34.94 to 10.48 after twelve weeks with a 70% improvement in the scores after twelve weeks i.e. second baseline visit($p<0.01$)**.**Tiredness was the most improved symptom. In contrast, no improvement was evident in the control group, rather a deterioration of scores particularly "tiredness', "feeling dizzy or giddy" was noticed. There was a 4% increase in the scores after twelve weeks of baseline visit ($p<0.01$) in the control group. Thyroid treatment satisfaction questionnaire (ThyTSQ) demonstrated a noticeable satisfaction in the scores after Levothyroxine supplementation at 6 weeks, which improved further at 12 weeks. In contrast the scores decreased slightly in the control arm. The changes in both the arms were found to be statistically significant. Kong. et. al [21] and Bono et. al. studied psychiatric symptoms in patients with mean TSH levels similar to the present study [7.72±1.53 µUI/mL and 8.5±5.7 µUI/mL, respectively][22]. These studies have reported that the reduced QoL of patients with hypothyroidism is often related to tiredness-the most frequently encountered symptom in our study too and the most improved symptom following Levothyroxine supplementation and behavioral changes, the next frequent symptom. Tiredness or fatigue is more commonly associated with poor physical domain scores, while behavior problems, especially depression

and mood changes are more commonly associated with poor mental health and thereby contribute to poor QoL among patients with hypothyroidism[16] To our knowledge, four studies with double-blind, placebo-controlled trial design evaluating QoL, have been published until now [21,23,24,25].Jaeschke *et.al*., described slight non significant improvement that was similar for Levothyroxine and placebo treated groups in all domains of QoL, as tested by the Chronic Thyroid Questionnaire (CTQ) and Sickness Impact Profile (SIP)[24].However,these authors included older participants with mean age of 68.0± 9.4 for L-T4 and 68.0±6.4 years for the placebo group, a considerably higher range than that of the present study. Elderly people usually have more complaints than younger counterparts, and these complaints may have etiologies other than thyroid dysfunction. Consequently, improvement with L-T4 may not have been detected. . Razvi *et. al*. published a double-blind placebo-controlled trial with an urban population of United Kingdom, with mean age of 53.8±12 years old and mean TSH level of 6.6 mIU/mL[25]. The authors applied the SF-36 score, but did not find any significant changes in health status both for Levothyroxine and placebo groups even after 12 weeks of treatment. In the same study, these authors did not observe any significant change in treatment satisfaction assessed by The Underactive Thyroid Treatment Satisfaction Questionnaire (ThyTSQ),.On the other hand, the authors observed reduced perception of the negative impact of hypothyroidism on total QoL with Levothyroxine substitution, using the Underactive Thyroid-Dependent QoL(ThyDQoL) .They also found a significant reduction in the frequency of patients reporting tiredness in the Underactive Thyroid Symptom Checklist (ThySC).

Early substitution with modest doses of Levothyroxine improves quality of life(QoL) significantly as compared to control population in subjects with Subclinical Hypothyroidism as evidenced in our study. The quality of life(QoL) as evaluated by patient reported outcomes, improved remarkably in the generic tool, as measured by SF36 questionnaire in all the following eight subscales "role physical" ,"physical function", "general health", "vitality" ,"mental health"," social function", "role-emotional" and "bodily pain". There also has been a significant improvement in the disease specific tools as measured by Underactive Thyroid Symptom Rating Questionnaire (ThySRQ) and Thyroid Treatment Satisfaction Questionnaire (ThyTSQ). However, long-term studies are required to confirm whether these apparent short-term benefits will translate into reduction in cardiovascular mortality and morbidity.

The present study had a few limitations. Firstly it was a pilot study consisting of 100 patients only (50 each in two groups). Though the treatment was for twelve weeks only, yet treatment duration was deemed adequate for the present study as it takes about 4-6 weeks of full replacement therapy with Levothyroxine to achieve stable euthyroidism. Still, it may be insufficient time for some other benefits (such as perceptible reduction in some symptoms and psychological factors) to become apparent to patients.

CONCLUSION

Subclinical hypothyroidism is a burning problem worldwide. It is widely being recognized as a potential cardiovascular risk factor that could interfere with overall morbidity and mortality. Our Indian patients with subclinical hypothyroidism had a significantly worse self perceived health status, compared to their normal counterparts. Thus, it is extremely crucial that physicians routinely assess the quality of life of patients with subclinical hypothyroidism, and plan to target improvements accordingly as an integral part of their management strategy. There is still controversy regarding indications of treatment in subclinical hypothyroidism. As the cost-effectiveness of the screening for mild thyroid dysfunction has already shown to be a favorable strategy, early and adequate treatment could yield improvements not only in the clinical and biochemical parameters but also on the quality of life. This data can be used to extrapolate newer innovative approaches for management and thereby creation of a guideline in the treatment of subclinical hypothyroidism particularly for subjects of Indian subcontinent in the forthcoming years.

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